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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YOUNG, SHAWQUIA	
ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/580,202	MANTLO ET AL.	
	Examiner	Art Unit	
	SHAWQUIA YOUNG	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,9-14,16,28,29,32-34,46,48,51,52,56,59,60,74,75,77,83 and 84* is/are pending in the application.

4a) Of the above claim(s) *9,10,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,11-14,16,28,29,32,46,48,51,52,56,59,60,74,75,77,83 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 3, 9-14, 16, 28, 29, 32-34, 46, 48, 51, 52, 56, 59, 60, 74, 75, 77, 83 and 84 are currently pending in the instant application. Applicants have withdrawn claims 9, 10, 33 and 34 in an amendment filed on January 29, 2008.

I. *Response to Arguments*

Applicants' amendment, filed on January 29, 2008, has overcome the following rejections and objections: the rejection of claims 3, 9-14, 16, 28, 29, 32, 33, 34, 46, 48, 51-52, 56, 74, 75, 77, 83 and 84 under 35 USC 112, second paragraph as being indefinite; the rejection of claims 46, 48, 75, 77, 83 and 84 under 35 USC 112, second paragraph as being indefinite; the rejection of claims 3, 9-14, 16, 28, 29, 32, 33, 34, 46, 48, 51, 52, 56, 74, 75, 77, 83 and 84 under 35 USC 112, second paragraph as being indefinite; the objection of claims 3, 9-14, 16, 28, 29, 32, 33, 34, 46, 48, 51, 52, 56, 74, 75, 77, 83 and 84 as containing non-elected subject matter; the objection of claims 74 and 75 because of informalities; the objection of claims 51, 75 and 77 because of informalities and the objection to the disclosure because of informalities. The above rejections and objections have been withdrawn.

The Examiner will rejoin and examine the method claims 59 and 60.

II. *Rejection(s)*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 11-14, 16, 28, 29, 32, 46, 48, 51, 52, 56, 59, 60, 74, 75, 77, 83 and 84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula **(Ic)**, stereoisomers and pharmaceutically acceptable salts of said compound does not reasonably provide enablement for a **solvate** or **hydrates** of a compound of formula **(I)**. The specification does not provide sufficient guidance nor does it enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case

The nature of the invention

The nature of the invention is a compound of formula Ic and stereoisomers or pharmaceutically acceptable salt thereof. There is no teaching of solvates and hydrates of the compounds of Formula Ic in the specification.

The state of the prior art and predictability or lack thereof in the art

It is the state of the prior art that the term "solvate" found in the claims is defined as a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute. It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compound (See *Vippagunta, et al.*)

The scope of "solvate" and "hydrate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates and hydrates cannot always be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular hydrate or solvate.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance present in the specification or working examples present in the specification are that defines or relates to what solvates are being included in the elected invention. The terms "solvates" and "hydrates" are not fully discussed in the specification.

The breadth of the claims

The breadth of the claims is a compound of Formula Ic, and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof.

The quantity of experimentation needed and the level of the skill in the art

While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to prepare compounds with various solvents without any direction as to what compounds form solvates with which solvents.

The level of skill in the art is high without showing or guidance as to how to make solvates of a compound of formula (I) it would require undue experimentation to figure out the solvents, temperatures and reaction times that would provide solvates of the above compounds.

To overcome this objection, Applicant should submit an amendment deleting the terms "solvates" and "hydrates".

Claims 59-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention is a method of treating metabolic disorder. Support for the intended use is based on in vitro binding at PPAR α receptors (pages 123 and 124) and in vivo data for the activation of the PPAR δ receptors (pages 131-133).

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of metabolic disorders by activating PPAR receptors would make a difference.

Applicants' claims are drawn to a method for treating metabolic disorder. A method for treating a metabolic disorder is a broad claim and thus encompasses a wide range of disorders, such as acid lipase disease, amyloidosis, Barth Syndrome, Farbers

Disease, etc. A metabolic disorder occurs when abnormal chemical reactions in the body disrupt the process of metabolism. The result could be that there are too much of some substances or too little of other ones in the body that are needed for a person to stay healthy. (See http://www.nlm.nih.gov/medlineplus/metabolicdisorders.html)

Applicants' claims are drawn to the treatment of acid lipase disease. Acid lipase disease occurs when the enzyme need to break down certain fats that are normally digested by the body is lacking or missing, resulting in the toxic buildup of these fats in the body's cells and tissues. Two lipid storage diseases caused by the deficiency of the enzyme lysosomal acid lipase: Wolman's disease and Cholesteryl ester storage disease (CESD) which both do not have a specific treatment. Certain drugs may be given to help with adrenal gland production and individuals with CESD may benefit from a low cholesterol diet. (See URL: http://www.ninds.nih.gov/disorders/acid_lipase.htm)

Applicants' claims are also drawn to the treatment of Barth syndrome. Barth syndrome is a rare congenital metabolic and neuromuscular disorder that affects boys. It is passed from mother to son through the sex-linked or X, chromosome. Symptoms affect multiple systems of the body and may include changes to metabolism, motor delays, hypotonia, delayed growth, hypoglycemia, etc. There is no specific treatment for Barth syndrome. (See URL: http://www.ninds.nih.gov/disorders/barth/barth.htm)

Metabolic disorders embrace a variety of disorders that involve different pathways and causes. Some of the largest classes of metabolic disorders are:

Disorders of carbohydrate metabolism

Disorders of amino acid metabolism

Disorders of organic acid metabolism

Disorders of fatty acid oxidation and mitochondrial metabolism

Disorders of porphyrin metabolism

Disorders of purine or pyrimidine metabolism

Disorders of steroid metabolism

Disorders of mitochondrial function

Disorders of peroxisomal function

Lysosomal storage disorders.

(See URL: http:/en.wikipedia.org/wiki/Metabolic_disorder)

Since Applicants have failed to disclose in the original specification what diseases or disorders are embraced by the term "metabolic disorder", the Examiner has interpreted that claims 59 and 60 read on any metabolic disorder.

Hence, in the absence of a showing of correlation between all the metabolic disorders encompassed by the claims as capable of treatment by activating PPAR receptors, such as one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the activation of PPAR receptors, for example, since it is no specific treatment for the metabolic disorder, Barth syndrome.

The amount of direction present and the presence or absence of working examples

The only direction or guidance present in the instant specification is minimal. There are no working examples present for the treatment of any metabolic disorder considered treatable by applicants' compounds.

Test assays and procedure are provided in the specification at pages 123-134 for binding and cotransfection studies; evaluation of triglyceride reduction and HDL cholesterol elevation in HuapoAI transgenic mice; evaluation of glucose levels in db/db mice; evaluation of the effects of compounds upon A^y mice body weight, fat mass, glucose and insulin levels; method to elucidate the LDL-cholesterol total-cholesterol and triglyceride lowering effect; method to elucidate the fibrinogen-lowering effect of PPAR modulators; method to elucidate the anti-body weight gain and anti-appetite effects of compounds of this invention; method to elucidate the activation of the PPAR delta receptor in vivo and efficacy studies.

Receptor activity is generally unpredictable and the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds in the treatment of metabolic disorders. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is drawn to a method of treating a metabolic disorder in a mammal. Applicants have failed to disclose what disorders are embraced by the term "metabolic disorders". Thus, Applicants method claims read on any metabolic disorder.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all metabolic disorders would be benefited by the activation of PPAR would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention in a method of treating a metabolic disorder. As a result necessitating one of skill to perform an exhaustive search for which diseases can

be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the method claims.

III. *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 5:30 AM-2:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shawquia Young/

/Kamal A Saeed, Ph.D./
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